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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,193	05/11/2001	Greta Van Den Berghe	6296.204-US	5893

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

NOTIFICATION DATE	DELIVERY MODE
06/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	09/853,193	VAN DEN BERGHE, GRETA	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36,62-65 and 87-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36 and 62-65* is/are rejected.

7)☒ Claim(s) *87-92* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 32-36, 62-65 and 87-92 are pending.

Applicant's amendment filed April 5, 2007 is acknowledged, and applicants' response has been fully considered. Claims 32, 35, 62 and 64 have been amended, and claims 40-44, 66-71 have been cancelled, and new claims 87-92 have been added. Therefore, claims 32-36, 62-65 and 87-92 are examined.

Withdrawn Claim Rejections - 35 USC § 103

2. The previous rejection of claims 40 and 41 under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Brange *et al.* (U.S. Patent 5,618,913), is withdrawn in view of applicant's cancellation of the claim in the amendment filed April 5, 2007.

3. The previous rejection of claims 40 and 42 under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Anderson, Jr. *et al.* (U.S. Patent 5,547,929), is withdrawn in view of applicant's cancellation of the claim in the amendment filed April 5, 2007.

4. The previous rejection of claims 43, 44 and 68-71 under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Havelund *et al.* (U.S. Patent 5,750,497), is withdrawn in view of applicant's cancellation of the claim in the amendment filed April 5, 2007.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 32, 33 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Brange *et al.* (U.S. Patent 5,618,913, published on April 8, 1997).

Scott *et al.* teach the use of a 24-hour infusion of saline (control) or a glucose potassium insulin (GKI) infusion (including 16 U of human soluble insulin, 20 mmole of KCl in 500 ml 10% dextrose) at 100 ml/h in the treatment of 53 acute stroke patients with mild or moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmole/L, corresponding to 126 and 307 mg/dL) in an explanatory, randomized, controlled trial to test safety, where no statistically significant differences is detected between the two groups at baseline (Table 1), and the GKI group had lower mean plasma glucose levels at 8 hours (6.4 mmole/L, corresponding to 115 mg/dL), 16 hours (6.5 mmole/L, corresponding to 117 mg/dL) and 24 hours (6.9 mmole/L, corresponding to 124 mg/dL) from the time starting infusion as compared to control, and the mean plasma glucose level is 9.1 mmole/L at zero time of infusion, which corresponds to 164 mg/dL (Table 2; Fig. 1; pages 794-796). The reference also indicates that of the patients in the GKI group, 21 (84 %) received 2400 mL infusate compared with 24 (96%) in the control group (page 795, second column); and the trial treatments were commenced by general and nursing staff, who monitored and maintained the infusions over next 24 hrs (page 794, second column). The acute stroke patients with no diabetes mellitus in their medical history (Table 1) are human non-diabetic critically ill patients (claims 62- 63). However, Scott *et al.* do not teach the use of an insulin analog in the treatment.

Brange *et al.* disclose some rapid-acting human insulin analogs such as Asp^{B28} human insulin having an improved property such as faster onset of action and reduced tendency to fibrillation as compared to insulin (column 1, lines 56-67; column 2, lines 51-58; claim 33).

At the time of invention was made, it would have been obvious that one of ordinary skill in the art has been motivated to combine the two references to use an insulin analog as taught by Brange *et al.* in a method of treating a critically ill patient having a blood glucose level of greater than 130 mg/dl as taught by Scott *et al.* (claim 32) because the use of an insulin analog would provide an improved property such as rapid-acting and reduced tendency to fibrillation as compared to insulin in the treatment (column 1, lines 56-67; column 2, lines 51-58 of Brange *et al.*). Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Response to Arguments

Applicants indicate claims 32 and 35 have been amended to now recite the phrase "wherein said insulin analogue is administered intravenously and continuously infused to said patient as needed for at least 24 hours and the blood glucose level is maintained for 24 hours or more." While Scott discloses an infusion period of 24 hours, Scott does not disclose methods of maintaining a desired blood glucose level via continuous infusion of insulin (or any GKI). Furthermore, Scott does not disclose the use of any GKI for the maintenance of a normal blood glucose level for greater than 24 hours (See page 794, second column; page 797, second column; Table 2; and Figure 2). Thus, Applicants assert that neither Scott alone, nor in combination with Brange, teaches or suggests the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection (pages 4-5 of the response).

Applicants' response has been considered, however, the arguments are not found persuasive because of the following reasons. Scott teaches that of the patients in the GKI group, 21 (84 %) received 2400 mL infusate compared with 24 (96%) in the control group (page 795, second column); and the trial treatments were commenced by general and nursing staff, who monitored and maintained the infusions over next 24 hrs and the treatment was administered through a peripheral vein in the nonparitic arm at a fixed rate of 100 mL/h via a metered infusion device (page 794, second column), these teachings indicate the treatment is carried out in continuous infusion for 24 hrs. Furthermore, Scott teaches that the GKI group had lower mean plasma glucose levels at 8 hours (6.4 mmole/L, corresponding to 115 mg/dL), 16 hours (6.5 mmole/L, corresponding to 117 mg/dL) and 24 hours (6.9 mmole/L, corresponding to 124 mg/dL) from the time starting infusion as compared to control (see Table 2 and Fig.1), which indicates the blood glucose level is maintained in a range from 60 mg/dL to about 130 mg/dL for 24 hrs. Thus, Scott in combination with Brange teaches or suggests the claimed invention. Therefore, the rejection is maintained.

6. Claims 32, 34 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Anderson, Jr. *et al.* (U.S. Patent 5,547,929, published on August 20, 1996).

Scott *et al.* teach the use of a 24-hour infusion of saline (control) or a glucose potassium insulin (GKI) infusion (including 16 U of human soluble insulin, 20 mmole of KCl in 500 ml 10% dextrose) at 100ml/h in the treatment of 53 acute stroke patients with mild or moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmole/L, corresponding to 126 and 307 mg/dL) in an explanatory, randomized, controlled trial to test safety, where no statistically

significant differences is detected between the two groups at baseline (Table 1), and the GKI group had lower mean plasma glucose levels at 8 hours (6.4 mmole/L, corresponding to 115 mg/dL), 16 hours (6.5 mmole/L, corresponding to 117 mg/dL) and 24 hours (6.9 mmole/L, corresponding to 124 mg/dL) from the time starting infusion as compared to control, and the mean plasma glucose level is 9.1 mmole/L at zero time of infusion, which corresponds to 164 mg/dL (Table 2; Fig. 1; pages 794-796). The reference also indicates that of the patients in the GKI group, 21 (84 %) received 2400 mL infusate compared with 24 (96%) in the control group (page 795, second column); and the trial treatments were commenced by general and nursing staff, who monitored and maintained the infusions over next 24 hrs (page 794, second column). The acute stroke patients with no diabetes mellitus in their medical history (Table 1) are human non-diabetic critically ill patients (claims 62- 63). However, Scott *et al.* do not teach the use of an insulin analog in the treatment.

Anderson, Jr. *et al.* disclose monomeric insulin analogs such as Lys^{B28}, Pro^{B29} human insulin having a property of ultra rapid time action profile as compared to insulin (column 1, lines 63-67; column 3, lines 2-18; claim 34).

At the time of invention was made, it would have been obvious that one of ordinary skill in the art has been motivated to combine the two references to use an insulin analog as taught by Anderson, Jr. *et al.* in a method of treating a critically ill patient having a blood glucose level of greater than 130 mg/dl as taught by Scott *et al.* (claim 32) because the use of an insulin analog would provide an improved property such as rapid-acting profile as compared to insulin in the treatment (column 1, lines 63-67; column 3, lines 2-18 of Anderson, Jr. *et al.*). Thus, the

combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Applicants use the same argument as in Scott in combination with Brange (page 5 of the response), regarding Examiner's response, please see the section above under paragraph 5.

7. Claims 35, 36 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott *et al.* (Stroke 30, 793-799 (1999)) in view of Havelund *et al.* (U.S. Patent 5,750,497, published on May 12, 1998).

Scott *et al.* teach the use of a 24-hour infusion of saline (control) or a glucose potassium insulin (GKI) infusion (including 16 U of human soluble insulin, 20 mmole of KCl in 500 ml 10% dextrose) at 100ml/h in the treatment of 53 acute stroke patients with mild or moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmole/L, corresponding to 126 and 307 mg/dL) in an explanatory, randomized, controlled trial to test safety, where no statistically significant differences is detected between the two groups at baseline (Table 1), and the GKI group had lower mean plasma glucose levels at 8 hours (6.4 mmole/L, corresponding to 115 mg/dL), 16 hours (6.5 mmole/L, corresponding to 117 mg/dL) and 24 hours (6.9 mmole/L, corresponding to 124 mg/dL) from the time starting infusion as compared to control, and the mean plasma glucose level is 9.1 mmole/L at zero time of infusion, which corresponds to 164 mg/dL (Table 2; Fig. 1; pages 794-796). The reference also indicates that of the patients in the GKI group, 21 (84 %) received 2400 mL infusate compared with 24 (96%) in the control group (page 795, second column); and the trial treatments were commenced by general and nursing staff, who monitored and maintained the infusions over next 24 hrs (page 794, second column). The acute stroke patients with no diabetes mellitus in their medical history (Table 1) are human

non-diabetic critically ill patients (claims 64-65). However, Scott *et al.* do not teach the use of an active derivative of an insulin analog in the treatment.

Havelund *et al.* disclose some active derivatives of insulin analogs such as des-Thr^{B30} human insulin γ Lys^{B29} tetradecanoyl having an improved property such as protracted profile of action and soluble at physiological pH as compared to insulin (column 2, line 27-column 3, line 43; claim 36).

At the time of invention was made, it would have been obvious that one of ordinary skill in the art has been motivated to combine the two references to use an active derivative of an insulin analog as taught by Havelund *et al.* in a method of treating a critically ill patient having a blood glucose level of greater than 130 mg/dl as taught by Scott *et al.* (claim 35) because the use of an active derivative of an insulin analog would provide an improved property such as prolonged action and soluble at physiological pH as compared to insulin in the treatment (column 2, line 27-column 3, line 43 of Havelund *et al.*). Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Applicants use the same argument as in Scott in combination with Brange (page 6 of the response), regarding Examiner's response, please see the section above under paragraph 5.

Claim Objections

8. Claims 87-92 are objected to because the claims are dependent from a rejected claim.

Conclusions

9. Claims 32-36 and 62-65 are rejected; and claims 87-92 are objected to.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner

CHIH-MIN KAM
PRIMARY EXAMINER

CMK
June 18, 2007